APPENDIX

Copies of cited publications (relevant pages):

USP 6,324,475 (Hayes) – cols. 7-8 and 19-20

USP 5,380,765 (Hirsch) – cols. 7-8

Prudhomme (1998) – pages 1 and 3

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FIG. 21 is a plot of threshold data using an ink-jet-based digital dispenser according to the present invention;

FIG. 22 is a schematic view of a long and short duration olfactory stimulus from an ink-jet based digital dispenser according to the present invention;

FIG. 23A is a schematic view of microreservoirs and manifolds attached to six parallel ink-jet channels;

FIG. 23B is a schematic view of an upper layer of a laser etched plate forming manifolds for the ink-jet channels shown in FIG. 23A;

FIG. 23C is a schematic view of a lower layer of a laser etched plate forming reservoirs for the ink-jet channels shown in FIG. 23A;

FIG. 24 shows human subject threshold tests for left, right and left and right combined nostrils conducted on the ink-jet-based digital dispenser illustrated schematically in FIGS. 3A and 3B;

FIG. 25 shows human subject threshold tests for left, right and left and right combined nostrils conducted on the ink-jet-based digital dispenser illustrated schematically in FIGS. 3A and 3B;

FIG. 26 is a schematic view of the dispersion of an olfactant in an airtube; and

FIG. 27 is a graph of the concentration of an olfactant versus time at 0.005 m from the source of the olfactant.

DESCRIPTION OF THE PREFERRED EMBODIMENT

As shown schematically in FIGS. 1A and 1B, the digital dispenser 10 of the present invention includes ink-jet microdispenser technology by incorporating piezoelectric transducer jets 12 which may be formed of piezoelectric material such as lead zirconate titanate (PZT). Those of ordinary skill in the art will recognize, however, that the piezoelectric transducer can be replaced by other transducers such as electrostrictive transducers, magnetostrictive transducers and electromechanical transducers. As shown in FIG. 1B, the digital dispenser 10 preferably includes eight piezoelectric microdispensing channels 12.

The test substances may be dispensed from reservoirs 16 in which test substance volume dispensing resolution preferably will be in the range of 200 picoliters. The test substances may include drugs, fragrances and volatile component containing substances. The test substances may also include nicotine for use in a cigarette withdrawal regimen.

The piezoelectric microdispensers 12 are integrated into individual, modular mechanical and hydraulic assemblies. These assemblies in turn are integrated into the airborne material delivery system. Conventional control electronics 14 and software design well known to those of ordinary skill in the art for use in solder microdispensing are used in the digital dispenser 10. The digital dispenser 10 according to the present invention permits the optimization of microdispenser operating parameters in terms of waveform and frequency for the airborne material/vehicle combinations.

According to a preferred embodiment of the present invention, water, ethanol and propylene glycol are used as the fluid vehicles for low concentration airborne material dispensing. All the test substances of interest are soluble in water, ethanol or propylene glycol, and none of the vehicles will interfere with olfactory thresholds for the 10 to 1000 picoliter dispensing volumes employed by the digital dispenser 10 of the present invention. The surface tensions and viscosities (magnitude and Newtonian vs. non-Newtonian) of the pure test substance solutions to be used are within the range such that their dispensing performance will be acceptable.

A schematic of the functional elements of the microdispensing device 12 of the digital dispenser 10 of the present invention is shown in FIG. 1C. As shown in FIG. 1C, the micro-dispensing device 12 incorporated in the device of the present invention includes a fluid fitting 18, a piezoelectric crystal 20, a glass tube 22 and an orifice nozzle 24. The fabrication technology and processes as well as the operating characteristics of this type of device are disclosed and claimed in U.S. Pat. Nos. 5,227,813, 5,235,352, 5,334,415, 5,345,256, 5,365,645, 5,373,314, 5,400,064, 5,402,162, 5,406,319, 5,414,916, 5,426,455, 5,430,470, 5,433,809, 5,435,060, 5,436,648 and 5,444,467, the entire disclosures of which are hereby incorporated herein by reference. The functional elements of the micro-dispensing device 12 of the digital dispenser 10 of the present invention as shown in FIG. 1C are integrated into a housing 26 that includes a fluid fitting as shown in FIG. 1A. This assembly is installed into a mechanical assembly that includes an electrical connector, fluid reservoir 16, and fluid filter. It also provides the mechanical reference surfaces for mating with the digital dispenser 10 of the present invention.

Airflow in the direction of the arrows shown in FIG. 1A is passive and is controlled by a subject's sniff or inhalation. The interface 28 to a subject preferably is similar to the output of a nasal inhaler, with one output for each nostril, although the interface may also have a single output for both nostrils. The total air volume for each channel preferably is less than 200 ml to insure that all of the airborne material is inhaled during a sniff (average of 0.5 liter/second flow rate during a 0.5 second sniff). Preferably a fan (not shown) and an activated charcoal filter 32 will be attached to the inlet 34 of the device 10 to provide a brief air purge to remove any residual test substance from the system between trials.

The dispensers 12 are targeted onto heated screens 36, preferably formed of platinum, to vaporize the test substance and vehicle. Preferably the platinum screens 36 are heated during the air purge between trials. A water dispenser 30 can be activated to humidify the air. Also, it is preferred that two heated platinum screens 36 are used to allow binasal testing.

If required, an aerosol blocking filter 38 may be included to filter aerosol particles (larger than 1 μm) that might be generated during high frequency multiple droplet dispensing events, due to later droplets impacting into a pool.

In a preferred embodiment, the digital dispenser 10 includes eight droplet generators. Each micro-dispensing device 12 is evaluated in a test stand with isopropanol being used as a test fluid. Droplet size and velocity as a function of drive voltage and frequency are measured for several frequencies. Droplet velocity is measured by stroboscopically "freezing" the drops in space and measuring the droplet-to-droplet distance (V=fλ) through a microscope. Drop size is measured by measuring the flow rate of the drop stream over a precise time interval.

Each test substance/vehicle solution of interest is tested for its microdispensing performance in the test stand over a range of concentrations. For threshold testing of the sense of smell, 3–4 orders of magnitude dynamic range (60–80 decismels), where:

$$1\ \text{decismel} = \frac{\log 10\ [\text{odor concentration}]}{20}$$

are needed. This is achieved by a combination of varying the concentration of the test substance in the vehicle and varying the amount dispensed. For example, the delivered mass requirements of one olfactory stimulation could require

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15-25 up and down intensity steps for a given threshold test, with a maximum of 3 threshold tests per subject.

Fragrances will be presented by microdispensing miniscule amounts into the vapor a subject is asked to sniff. Five minute breaks will be given between tests (more frequently if requested), and no more than 45–60 minutes total testing will be done per subject.

The subject population at SMU will be drawn from the entire student body, which is 95% between the ages of 17 and 23, 52% female, and 22% minorities, of whom approximately 10% are African American, and the remainder are predominantly of Hispanic, Asian, and Native American origin.

The subject population at UC-Irvine will be drawn from normal and Alzheimer's diseased aged subjects, ranging from 55 to 85 years of age. This group is approximately 50% female.

EXAMPLE 4

The digital dispenser **10** of the present invention will permit the probing of new dimensions of human olfaction. The analytical capability of the digital dispenser **10** can be used to understand how olfactory signals are summed over time (to the millisecond range) and (when combined with endoscopic presentation) over the space of the olfactory epithelium. Thus, presenting brief "clouds" of airborne molecules or droplets allows exploration of the temporal integration (approximately 100 ms) and, with endoscopic systems, the spatial integration (approximately 10,000 to 100,000 square microns of olfactory epithelium or the vomeronasal organ) of sensory responsiveness of the olfactory epithelium and the vomeronasal organ (which is specially tuned to pheromones).

The resolution of these basic psychophysical issues will allow the determination of the most reliable and most useful patterns to use for diagnostic work. By injecting miniature "clouds" of airborne molecules or droplets into the inspired airstream, olfactory stimuli can be delivered that are very brief, relative to the overall duration of a voluntary sniff (about 0.5 seconds in duration) or an inhalation (2–4 second duration). This is shown schematically in FIG. 22. Actual examples of such temporal "sculpting" of the gas stimulus are shown in FIG. 7. There will be some smoothing of these temporal functions, due to turbulence as air flows through the nasal meatuses and around the turbinate bones. Retention and release of test substance molecules on the airway surfaces will also produce some temporal smearing of the olfactory stimulus. Still, a temporal dimension will be introduced into olfactory testing by the microdispensing of airborne molecules or droplets into the inlet of the nostrils.

The digital dispenser **10** of the present invention will allow a determination of empirical data such as what temporal patterns of stimulation during a single sniff or single inhalation give the strongest subjective response (i.e., lowest "threshold" or largest d' of a Receiver Operating Curve), how responses from the two nostrils are integrated, what the time-constants are for inter-nostril integration, whether there is an olfactory directional sense, whether there is a dominant hemisphere when dissimilar airborne materials are presented to the two nostrils, whether there is a directionality of olfactory signals due to inter-nostrils differences, whether concentration and duration will be interchangeable (for a fixed total number of airborne materials) over about 600 milliseconds, with little further integration thereafter and whether different airborne materials give different integration functions, as is the case with different adaptation functions for different airborne materials.

The results of these determinations will yield a normative baseline for novel areas of human performance that will provide sensitive indicators of neuropathology. The digital dispenser can be configured as a hand-held device to be used by a clinician in the office (or even in the field) that can precisely probe for within and between nostrils effects. In view of the possibility that olfactory asymmetries could be useful predictors of brain disease, these studies could lead to a practical and powerful olfactory diagnostic tool.

The choice of test substances to be loaded in the microjets **12** include, but are not limited to, pyridine, eugenol, 1-butanol and mercaptan which are commercially available from International Flavors and Fragrances, Inc. as well as some test substances shown to be especially difficult to identify for patients with Parkinson's and Alzheimer's such as cinnamon, chocolate, strawberry and pizza which are commercially available from 3M Microfragrances. Other test substances are disclosed in Table 3 in Amoore, J. E. (1991): Specific anosmias in *Smell and Taste in Health and Disease*, ed. by T. V. Getchell et al., Raven Press, New York, pp. 655–664, the entire disclosure of which is incorporated herein. These other substances include: fruity (isoamyl acetate), etherish (methyl ethyl ketone), camphor (1,8-cineole), clove (eugenol), cinnamon (cinnamaldehyde), minty (1-carvone), thyme (thymol), rosy (2-phenylethyl alcohol), citrous (geranial), floral (phenylethyl methyl ethyl carbinol), lily (lyral), violet (β-ionone), vanilla (vanillin), amber (thujaamber), musky (ω-pentadecalactone), garlic (allicin), fishy (trimethylamine), halogen (iodoform), burnt (pyridine), phenolic (4-ethylphenol), sweaty (isovaleric acid), urinous (5α-androst-16-en-3-one), repulsive (phenylisocyanide), spermous (1-pyrroline), fecal (skatole), resinous (isoamyl alcohol), gassy (tert-butyl mercaptan), acid (acetic acid), buttery (2,3-butanedione), earthy (2-methylisoborneol), vegetable (methional), cyanide (hydrogen cyanide), malty isobutyraldehyde), sulfide (hydrogen sulfide) and armpit (trans-3-Methyl-2-hexenoic acid).

Still other test substances include: peanut, soap, paint thinner, motor oil, smoke, lemon, menthol, onion, licorice, wintergreen, orange, lilac, grape, gasoline, bubble gum, chocolate, mint, root beer, cherry, strawberry, fruit punch, rose, turpentine, pine, pizza, watermelon, grass, natural gas, cinnamon, pineapple, coconut, dill pickle, clove, banana, garlic, peach, lime, leather, gingerbread, cheddar cheese, musk, cedar, apple, black pepper, chili, tomato, pumpkin pie, skunk, whiskey and honey.

The concentration of test substance and the temporal envelope of presentation, as well as the inter-nostrils differences can all be controlled by merely changing the number of digitally-controlled microdrops to be dispensed into the airstream. In all cases, the maximum mass of airborne materials injected into the airstream will be kept well below the saturation point, so that condensation of the test substances onto the air passages will be minimized.

For a typical logarithmic series of test substance intensities, the dispensers **12** can dispense increasing masses of test substance by increasing the number of drops dispensed. Jetting at 1 to 10,000 drops/second, a single jet **12** can dispense over a 4 log-unit range of test substance intensity in 1 second. For greater temporal compression, jets **12** with differing concentrations can be used. For most test substances, a range of 40 decismels (100-fold concentration range) includes the thresholds of about 98% of all subjects (i.e., ±2 standard deviations), so that 80 decismels (10,000-fold) is more than an adequate dynamic range for the system.

The test subjects will hear an audible "beep," informing them to start an inhalation (or sniff), and the airborne

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tification and sensitivity to 40 stimuli using scratch and sniff cards. Each subject rated the fragrance samples by scratching with a pencil included with the test cards, sniffing, and then identifying the odorant as one of four choices. A label could be repeatedly scratched as needed before moving to the next odorant and returning to previous odors was allowed.

The results of the patient's score on the Smell Identification Test™ were evaluated by reference to the established normal values for age and gender provided in the *Smell Identification Test™ Administration Manual* on pages 19 and 20. The patient's total number of correct responses (maximum of 40) was established by use of the test's scoring key. The patient's test score is located in the far left hand column of Table 1 for women and Table 2 for men. The age group is located along the top of the table and the subject's percentile score is read at the intersection of test score row and age group column. The percentile value reflects the percentage of normal patients having that score.

A diagnosis for an olfactory dysfunction is made by identifying whether the person's test score falls within the anosmia (total inability to perceive odor) or microsomia range (decreased smell ability). Generally, scores falling in the following ranges are indicative of smell dysfunction:

Smell Identification Test Score	Olfactory Diagnosis
0–5	Probable malingering
6–19	Total anosmia
20–33	Microsomia (males only)
20–34	Microsomia (females only)
34–40	Normosmia (males only)
35–40	Normosmia (females only)

The unilateral threshold test was conducted according to standard methods as described by J. Amoore et al., *Rhinology*, 21-49-54 (1983). Briefly, the patient's ability to detect increasing amounts of carbinol, PD-lactone, cineole, thiophane, pyridine, (PE-phenol), and CA-phenone in the left and right nostrils was tested. The standards in decismels were obtained from OlfactoLabs, El Cerrito, Calif. For example, the threshold level of PE phenol detected by a patient was determined by presenting the patient with 64 different bottles of different concentrations of PE-phenol. The patients were presented with bottles of different concentrations compared to the blank and asked to identify the bottle with the substance. The patient was presented with the bottles in random order and needed to correctly identify the substance three times in order to identify the patient's threshold concentration. The level at which the patients in the study detected each of the compounds was compared to known or expected values. The standard samples from OlfactoLabs were already calibrated in decismels. If the amount detected by the patient was lower than the expected values, the patient was more sensitive to the compound and detected the chemosensory agent at a negative decismel value. If the amount detected known was greater than the expected value, the patient was less sensitive to the compound and detected the chemosensory agent at a positive decismel value.

Odor thresholds are expressed on the "decismel scale". The mean threshold concentration of a chemosensory agent detected by a control group of 20-year olds is set at the 0 value. A decismel is calculated by dividing the concentration of the chemosensory agent detected by the patient to the normal threshold concentration (using the published value or empirically determining the value) and then taking the logarithm of the quotient. The logarithm of the quotient is then multiplied by 20 to obtain the decismel value. Decismel values can be positive or negative. A positive decismel value indicates the patient is less sensitive to the chemosensory agent, i.e. has a higher threshold detection concentration. A negative decismel value indicates that the patient is more sensitive to the compound, i.e. has a lower threshold detection concentration. An increase in the threshold concentration value over the mean threshold concentration value of twofold corresponds to 6 decismels. The suggested thresholds for hyposmia are 30 ds and of functional anosmia at 54 ds. The normal mean threshold values for each chemosensory agent are known and can be used to convert the threshold concentration into decismels. A change of at least 5 ds from the expected value was considered a significant change in the threshold level of detection of the compound.

The Accusens T Test® was conducted according to standard methods as described by the *Accusens T™ Taste Function Kit Manual*. Briefly, the ability of the patients to taste sodium chloride (NaCl), sucrose, hydrochloric acid (HCl), urea, and phenylthiocarbamide (PTC) was evaluated by the patients tasting solutions containing increasing amounts of the compound.

The ability of the patients to detect and recognize the type and intensity of the solution was measured. Two drops of each of three solutions was placed on a patient's tongue successively. Two of three solutions were water and one of the solutions was either salty (NaCl), sweet (sucrose), sour (HCl) and bitter (PTC). Three different concentrations of salt, sucrose and HCl were tested. The PTC test was the last test performed. The patient was instructed to identify which one of the three solutions was different, whether it was salty, sweet, sour or bitter, and to estimate the degree of the taste on a scale of 1 to 100. All three judgments must be correct for diagnosis of normal taste. If the patient could not detect correctly the different tastant or recognize each tastant, the next higher concentration of the tastants was tested in the same manner until the patient correctly identified the tastants. The patient's responses were compared to established values for normal taste detection and recognition provided in the test kit. Any failure to detect or recognize the tastants is indicative that the patient has hypogensia.

If the patient correctly detects and recognizes all of the tastants but gives intensity responses less than 5%, then a second test is done. Patients taste each of three different concentrations of the NaCl solution, sucrose solution and HCl solution and rate the intensity of each of the solutions. Responses considered normal for the lowest concentration are 5% to 15%, responses considered normal for the middle concentration are 10% to 30% and responses considered normal for the highest concentration are 25% to 50%. Any response lower than the lower percentage of the ranges noted above is abnormal and indicative of hypogensia.

The patients also were evaluated for psychiatric disorders using the MMPI-II, the MCMI-II, and the Beck Depression Inventory. The MMPI-II is available from National Computer Systems and is administered according to standard methodologies as described in *Psychological Assessment with the MMPI*, A. Friedmann et al., editor, Laurence Erlbaum Assoc., publishers (1989) at

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Acute-Onset Persistent Olfactory Deficit Resulting from Multiple Overexposures to Ammonia Vapor at Work

Janice C. Prudhomme, DO, MPH, Dennis J. Shusterman, MD, MPH, and Paul D. Blanc, MD, MSPH, University of California, San Francisco, Calif.

J Am Board Fam Pract 11(1):66-69, 1998.

Introduction

Impaired olfaction (a functional decrement in the sense of smell) is not uncommon. It is estimated that at least 2 million Americans suffer from an impaired sense of smell, although the actual number is probably higher.[1] The importance of this primary sense should in no way be minimized, since its absence can result in profound consequences. Both personal protection and quality of life can be compromised by impaired olfaction. Intact olfaction provides an excellent warning system for detection of hazardous conditions including smoke from fires, ingestion of spoiled foods, and hazardous materials encountered on the job. An employee lacking intact olfaction could be seriously impaired in certain settings, and indeed might be precluded from selected duties as a result. Even appropriate respiratory protection (ie, air-purifying respirators) might not offer sufficient assurance against toxic exposures because the impaired person would not be able to detect respirator leaks or cartridge breakthrough.[2] The senses of taste and smell are intertwined; loss of smell can adversely affect gustatory pleasure or, more importantly, can lead to anorexia.

Despite the frequency of irritant upper airway exposures occupationally,[3] published cases of work-related residual olfactory impairment have frequently lacked documentation of sensory testing. Recognition of the link between irritant exposure and upper airway functional loss is thus important to occupational and general health practice.

We report a case in which persistent hyposmia (reduction in the sense of smell) occurred following an acute industrial exposure to ammonia.

Case Report

A 41-year-old man was in his usual state of good health until 1993, when he was acutely overexposed to an ammonia leak while employed as the owner-operator of a fish-processing plant. The aqueous ammonia involved in the leak was used as a refrigerant in the fish-processing operation. No other irritant gases, including sulfur dioxide, were used as refrigerants in the operation. At the time of the leak, the patient experienced eye and nasal irritation and mild facial skin burning. He avoided mouth breathing and denied experiencing any other acute respiratory symptoms. He spent an entire morning in the vicinity of the leak without wearing respiratory protection. He had previously experienced ammonia leaks with similar but less severe symptoms. No quantitative industrial hygiene measurements of the ammonia concentration were made.

In contrast to previous ammonia exposures, after this incident the patient's nasal symptoms persisted, marked by a sense of nasal stuffiness and intermittent epistaxis continuing for 2 weeks. Although the nasal congestion later resolved, he also complained of a concomitant, complete loss of smell that improved only minimally. Whereas some sense of smell did return, he noticed difficulty recognizing previously familiar odors, such as his wife's perfume or freshly mowed grass. Foul or unpleasant odors did not replace normal smells. No other nasal or respiratory tract symptoms, such as rhinorrhea or discharges, persisted. His sense of taste returned to baseline after a transient complaint of a metallic taste.

His senses of hearing and vision remained intact. He reported no history of atopic disease, including allergic rhinitis. He was a lifetime nonsmoker and was on no medications at the time of exposure. There was no history of nasal trauma related to his symptoms. He was examined by an otolaryngologist 6 months after the acute exposure; no structural abnormalities were observed. A brief trial of intranasal flunisolide was prescribed with no effect.

When he was examined 30 months after his acute exposure, his external nares were patent and without apparent abnormality. Bilateral nasal breathing was without deficit, and there was no sinus tenderness to palpation. Findings of the oropharynx and

chemically-induced olfactory dysfunction. More interestingly, of these 7 patients, 3 (43 percent) had the onset of their hyposmia following exposure to ammonia. Details of the exposure are briefly described for only one of the three incidents. In the described case, an acute, overwhelming ammonia exposure caused a severe intranasal burn and ultimately irreversible hyposmia. As in our case, there was no response to a trial of nasal steroids. This case series provides additional support that ammonia can adversely impact olfaction.

A syndrome known as the reactive upper airways dysfunction syndrome, or RUDS, might tangentially apply to our case. The syndrome helps categorize persons who experience persistent nasal symptoms, specifically rhinitis and heightened subjective sensitivity to chemical irritants, after a single acute exposure to an upper respiratory tract irritant.[30] This syndrome is considered analogous to an asthma-like syndrome known as RADS (reactive airways dysfunction syndrome) that develops in certain persons following acute pulmonary tract irritation.[31] Symptoms develop after a single (generally, intense) exposure and persist in the absence of additional exposures. Our patient did develop some pertinent nasal symptoms following one of multiple acute exposures to ammonia. Although an olfactory deficit as such has not been incorporated into the clinical syndrome definition of RUDS,[30] it is a plausible consequence of any persistent inflammatory process.

A major limitation in earlier reports of olfactory impairment following environmental exposure has been the lack of objective, standardized measurements of olfactory function. The two tests used in this case, UPSIT (University of Pennsylvania Smell Identification Test), a qualitative test kit, and OLFACTO-LABS (Quantitative Smell Test Kits) are well-validated[32,33] and are now widely available.

The upper respiratory tract is inherently susceptible to the toxic effects of airborne irritants. The nasal mucosa and olfactory epithelium are primary targets of water-soluble toxicants, of which ammonia is prototypic. Such exposures and their resulting impairment are likely far more commonly encountered in primary care settings than is generally appreciated. It has recently been reported, for example, that family physicians spend 14 percent of their time dealing with occupational health problems overall.[34] Upper airway disorders, including irritant-related symptoms, are an important occupational problem among those likely to be encountered. In the same study, 29 percent of physicians specified occupational exposures as a high-priority issue about which more knowledge was needed. Knowledge on olfactory impairment is a particularly needed area of better understanding.

* Decismels (dS) are defined as 20 log (test concentration/reference concentration), where the reference concentration is the average odor threshold in a reference population. Thus, a score of 40 dS indicates that the patient's odor detection threshold was at a test concentration 100 times the population average for the compound employed.

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8/25/2005